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The formation of poly(ester–urea) networks in the absence of isocyanate monomers

Jörg Zimmermann^a, Ton Loontjens^b, B.J.R. Scholtens^b, Rolf Mülhaupt^{a,*}

^a *Institut für Makromolekulare Chemie und Freiburger Materialforschungszentrum FMF der Albert-Ludwigs-Universität, Stefan-Meier-Strasse 21/31, D-79104 Freiburg, Germany*

^b *DSM Research, 6160 MD Geleen, Netherlands*

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Abstract

The polymerization of *N,N'* carbonylbis (caprolactam) (CBC) and polyol in the presence of alcoholate as catalyst produced cross-linked poly(ester–urea)s via ring opening addition reaction. In contrast to conventional synthetic routes, the use of non-toxic CBC eliminates the need for toxic isocyanate-based monomers. The structure of the molecules resulting from model reactions was confirmed using FT-IR and ¹H- and ¹³C-NMR spectroscopy. Poly(ester–urea) networks exhibit rubber-like mechanical properties and high-temperature stability. Cell adhesion and cell growth on the polymers evidenced the high biocompatibility of the material. Degradation of the poly(ester–urea)s was investigated at 70°C in neutral and basic aqueous solution. The degradation depends on the swelling behavior of the samples. Mechanical properties, good biocompatibility, and degradation behavior of the CBC/polyol-based polymers make them interesting materials for biomedical applications.

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Keywords: Poly(ester–urea); *N,N'* carbonylbis (caprolactam); Cell adhesion; Polymer network; Degradation

1. Introduction

Synthetic biocompatible and bioresorbable polymers such as poly(α -hydroxy acid)s, poly(α -amino acid)s and poly(ester–urethane)s have become increasingly important for the development of temporary surgical and pharmaceutical devices like wound closure devices, vascular prostheses or sustained drug delivery systems [1–4]. Bioresorbable poly(ester urethane)s and poly(ester–urea urethane)s have been synthesized and widely used in medical devices [5–7]. However, some of these polymers were observed to produce toxic by-products which have posed severe limitations on their use in vivo. For example, urethane formed by reacting poly(D,L-lactide) diol with methylene diisocyanate hydrolyzes in vivo into 4,4-diamintoluene, which reportedly causes hepatitis in humans [8,9]. The hydrolytic resistance of poly(ether–urethane–urea)s and poly(ester–urethane–urea)s was also investigated [10].

Nevertheless, except for toxicity of isocyanate monomers or degradation products of the polymers, urethanes and urethane ureas possess unique properties which make them ideal for tissue engineering applications. These properties include a wide range of physical and mechanical properties, chemical functionality, and diversity in specific polymer characteristics.

In our work, we have developed a new isocyanate-free synthetic route to poly(ester–urea)s which is based on polyols commonly used in poly(urethane) chemistry. The reaction of CBC and alcohol using alcoholate as catalyst was investigated. This reaction was used for the preparation of poly(ester–urea) networks. The networks were investigated with respect to their mechanical properties, temperature stability, hydrolytic resistance, biocompatibility and support of cell growth in vitro.

2. Experimental

N,N' carbonylbis (caprolactam) (CBC) (DSM), methanol (Fluka), ethanol (Fluka), 2-propanol (Fluka) and sodium hydride (Fluka) were used as received.

*Corresponding author. Tel.: +49-761-203-6273; fax: +49-761-203-6317.

E-mail address: mulhaupt@uni-freiburg.de (R. Mülhaupt).

Baygal[®] K55 ($M_n = 440$ g/mol) (Bayer) and Baygal[®] K390 ($M_n = 4800$ g/mol) (Bayer), both tri-hydroxy functionalized block copolymers of poly(propylene oxide) with poly(ethylene oxide) end segments, were dried in a vacuum mixer at 80°C for 5 h.

2.1. Model reaction of CBC and alcohols with alcoholate catalysis

The reaction of CBC with methanol exemplifies the model reactions of CBC. The reaction was performed as follows: 0.4 ml (10 mmol) methanolate solution (4%), prepared by stirring of 2.45 g potassium in 250 ml of methanol, were added to a solution of 2.52 g (10 mmol) CBC in 10 ml methanol. The mixture was stirred for 10 h at ambient temperature. Then 3 g of acidic ion exchange resin Amberlite IR 120 (Fluka) was added to neutralize the reaction mixture. After 15 min the ion exchange resin was filtered off and the solvent was removed in vacuo. The product was dried in vacuum at 60°C and characterized without purification by ¹H-NMR, ¹³C-NMR, FT-IR spectroscopy and melting point measurements.

6,6'-uretylene-di-hexanoic acid dimethyl ester (**3a**): $C_{15}H_{28}N_2O_5$ (316 g/mol); mp: 101–103°C, IR: 1730 cm⁻¹, (s C=O ester), 1617 cm⁻¹, (s C=O urea), 1576 cm⁻¹, (s amide II, urea); ¹H-NMR: $\delta = 4.7$ (t, 10, 13), 3.6 (s, 2, 21), 3.1 (q, 9, 14), 2.2 (t, 5, 18), 1.6 (m, 8,

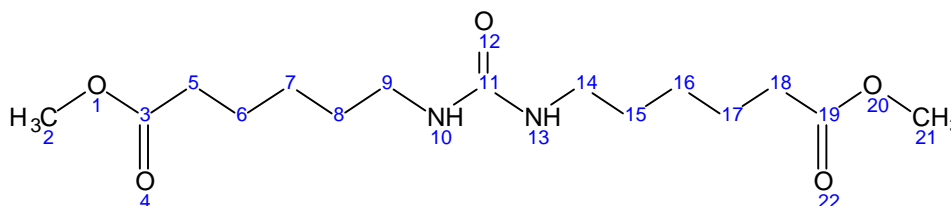
15), 1.4 (m, 6, 17), 1.3 (m, 7, 16); ¹³C-NMR: $\delta = 174.0$ (19, 3), 158.6 (11), 51.4 (2, 21), 40.0 (14, 9), 33.8 (5, 18), 29.9 (8, 15), 26.3 (6, 17), 24.5 (7, 16) (Scheme 1).

6,6'-uretylene-di-hexanoic acid diethyl ester (**3b**): $C_{17}H_{32}N_2O_5$ (344 g/mol); mp: 64–66°C, IR: 1734 cm⁻¹, (s C=O ester), 1617 cm⁻¹, (s C=O urea), 1589 cm⁻¹, (s amide II, urea); ¹H-NMR: $\delta = 4.1$ (q, 22, 2), 3.1 (t, 10, 15), 2.2 (t, 6, 19), 1.6 (m, 9, 16), 1.5 (m, 7, 18), 1.3 (m, 8, 17), 1.2 (t, 3, 23); ¹³C-NMR: $\delta = 173.7$ (20, 4), 158.9 (12), 60.2 (2, 22), 40.2 (15, 10), 34.1 (6, 19), 29.7 (9, 16), 26.3 (7, 18), 24.4 (8, 17) (Scheme 2).

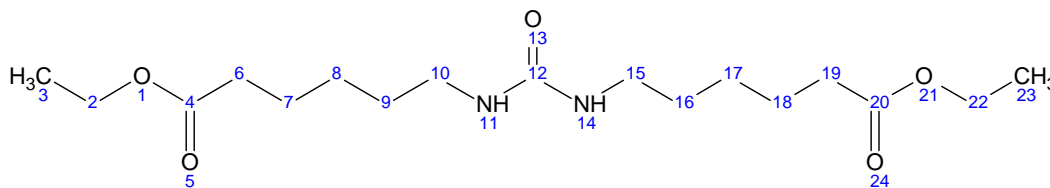
6,6'-uretylene-di-hexanoic acid diisopropyl ester (**3c**): $C_{19}H_{36}N_2O_5$ (372 g/mol); mp: 58–59°C, IR: 1731 cm⁻¹, (s C=O ester), 1617 cm⁻¹, (s C=O urea), 1572 cm⁻¹, (s amide II, urea); ¹H-NMR: $\delta = 4.9$ (m, 2, 23), 4.5 (t, 12, 15), 3.1 (q, 11, 16), 2.2 (t, 7, 20), 1.6 (m, 10, 17), 1.5 (m, 8, 19), 1.3 (m, 9, 118), 1.2 (d, 3, 6, 24, 26); ¹³C-NMR: $\delta = 173.2$ (21, 4), 158.4 (13), 67.5 (2, 23), 40.2 (11, 16), 34.5 (7, 20), 29.8 (10, 17), 26.3 (8, 19), 24.6 (9, 18), 21.8 (3, 6, 24, 26) (Scheme 3).

2.2. Preparation of CBC-based poly(ester–urea) networks

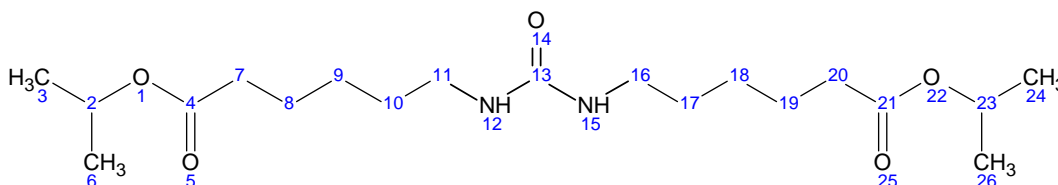
As an example, the synthesis of a polymer network containing 77.2 wt% Baygal K390, 8.6 wt% Baygal K66 and 14.2 wt% CBC is described. 16.54 g (65.6 mmol) solid CBC were mixed with 90 g (18.75 mmol) Baygal



Scheme 1. 6,6'-uretylene-di-hexanoic acid dimethyl ester (**3a**).



Scheme 2. 6,6'-uretylene-di-hexanoic acid diethyl ester (**3b**).



Scheme 3. 6,6'-uretylene-di-hexanoic acid diisopropyl ester (**3c**).

K390. After heating to 120°C for 5 min the homogenous mixture was cooled to 40°C under stirring. About 10 g (22.7 mmol) partially deprotonated Baygal K55, prepared by adding 138 mg (5.75 mmol) sodium hydride to 10 g (22.7 mmol) Baygal K55, were added and the mixture was stirred for further 5 min. The transparent mixture was poured into a heated (50°C) mould (200 mm × 200 mm × 4 mm) and cured at 50°C for 10 min and 125°C for 15 h.

3. Cell adhesion experiments

The suitability of hydrogels for cell adhesion was investigated using a human fibroblast cell line (HS27). Cell adhesion was monitored by direct observation in an inverted microscope after staining the cells with propidium iodide. The experimental procedure was the following: Thin slices of the investigated hydrogels were immersed in 70% ethanol for 30 min for sterilization and subsequently equilibrated with cell culture medium (DMEM, Gibco). At day 1, cells were seeded in a density of 40,000 cells per cm² in a volume of 50 µl on top of the hydrogel surface. After 1 h incubation in a humidified incubator at 37°C equilibrated with 5% CO₂, 2 ml of cell culture medium (DMEM supplemented with 10% fetal bovine serum, penicillin 100 U/ml and streptomycin 100 µg/ml) were carefully added to each well. Gels containing cells on their surface were incubated in a humidified incubator at 37°C equilibrated with 5% CO₂. At day 4, staining with propidium iodide was performed to visualize viable adherent cells. Briefly, gels were fixed in ice-cold 70% ethanol for 10 min. After washing with phosphate buffered saline (PBS) (3 × 5 min), the gels were incubated in a propidium-iodide solution (8 µg/ml in PBS) in the dark for 30 min. After a second washing step (3 × 5 min in PBS), nuclear staining was evaluated using a fluorescence microscope (excitation 510–560 nm).

FT-IR: FT-IR spectroscopy was carried out using a Bruker IFS 88 spectrometer equipped with a temperature chamber and a Golden Gate single reflection ATR unit.

TGA: Thermogravimetric analysis (TGA) measurements were performed using a Netzsch STA 409 with a heating rate of 10 K/min and N₂ atmosphere.

NMR: ¹H- and ¹³C-NMR spectra were recorded in CDCl₃ at concentrations of 100 mg/ml on a Bruker ARX 300 spectrometer, operating at 300 and 75.4 MHz, respectively.

Melting point: Melting points were determined using a Büchi Melting Point B540 apparatus.

DSC: Differential scanning calorimetry measurements were performed on a Perkin Elmer DSC-7. Glass transition temperatures (*T_g*) are taken from the second heating run at a heating rate of 10 K/min. The

measurements were performed from –100°C up to 30°C.

Flexural strength and module: These were measured using an Instron 4204 universal testing machine. The measurements were performed according to ISO 527/95 using samples in the dry state.

4. Results and discussion

4.1. Reaction behavior of CBC with alcohols using alcoholate as catalyst

The reaction behavior of CBC with alcohol is not described in literature. For the reaction of CBC with amines two different reaction behaviors, the opening and the substitution of caprolactame, are known [11]. As model reactions the conversion of CBC with methanol, ethanol and 2-propanol using the respective alcoholate as catalyst was investigated. The reaction of CBC with different alcohols is shown in Fig. 1.

¹H-NMR and FT-IR spectroscopy were used to obtain quantitative information on the reaction. The reaction of CBC and alcohol in the presence of the corresponding alcoholate as catalyst occurs by quantitative ring opening addition of two equivalents of alcohol. This reaction behavior was observed for methanol, ethanol and 2-propanol. No side reactions

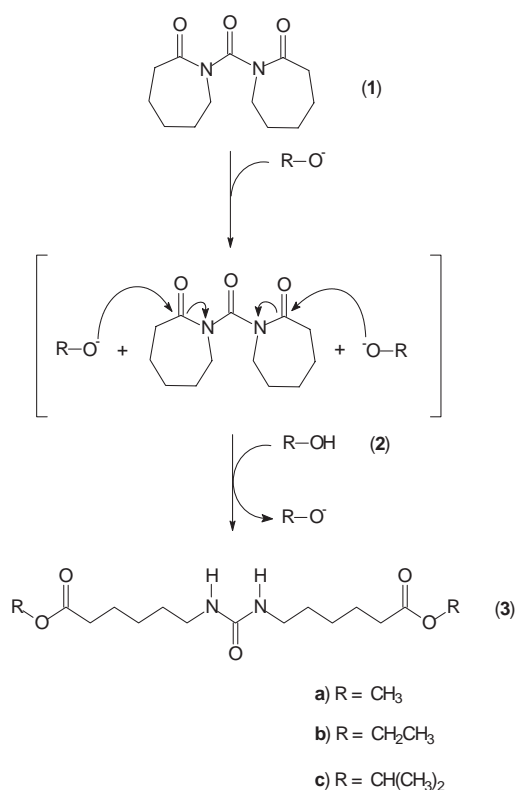


Fig. 1. Reaction behavior of CBC and alcohols using alcoholate as catalyst.

were observed at ambient temperature, a purification of the products was not necessary. Fig. 2 shows the ^1H -NMR spectrum from the product obtained by reacting CBC with methanol, under methanolate catalysis.

All ^1H -NMR signals of CBC at 3.8, 2.6, 1.8 and 1.7 ppm disappear. New signals of the adduct are observed at 4.7, 3.6, 3.1, 2.2, 1.6, 1.4 and 1.3 ppm. Fig. 2 demonstrates that the reaction between CBC and methanol occurs by ring opening addition reaction, thus producing (3a) in quantitative yield. Additional characterization by FT-IR and melting point measurement provides additional experimental evidence for the formation of 6,6'-uretylene-di-hexanoic acid dimethyl ester. The melting point of (3a) corresponds to the value found in literature [12]. From the reaction of CBC with ethanol and 2-propanol, we obtained the corresponding addition products in quantitative yield. This confirms that CBC reacts with alcohol under alcoholate catalysis by a ring opening addition reaction. Physical data of the addition products of CBC and methanol (3a), ethanol (3b), and 2-propanol (3c), are given in the experimental part.

4.2. Polymerization

We used the described ring opening addition reaction of CBC with hydroxy groups for the preparation of polymer networks based on commercial triols usually used in polyurethane formulations. The reaction of CBC with polyols occurs in analogy to the reaction of diisocyanate and polyol in polyurethane chemistry. In

contrast to the formation of urethanes in conventional polyurethane chemistry, the substitution of diisocyanates for CBC results in the formation of poly(ester-urea)s. Two different polypropylene oxide-based triols Baygal K55 ($M_n = 440$ g/mol) (PPO1) and Baygal K390 ($M_n = 4800$ g/mol) (PPO2) were used. The compositions and properties of the polyols are listed in Table 1.

CBC was dispersed in stoichiometrical amounts of the polyols and heated to 120°C under stirring to obtain a homogenous solution. The mixture was cooled to 40°C and activated with 4 mol% alcoholate prepared by the addition of sodium hydride and the corresponding polyol. The activated formulation was stirred for additional 10 min and filled into a heated (50°C) mould ($200\text{ mm} \times 200\text{ mm} \times 4\text{ mm}$). The samples were cured at 50°C for 10 min and 125°C for 12 h. Pot time of the activated formulations at ambient temperature was in the range of 30 min. The pot time strongly depends on the amount of alcoholate and formulation temperature. The described reaction behavior of CBC and polyols occurs quantitatively at ambient temperatures, at higher

Table 1

Composition and properties of the used polyols

	Baygal K55	Baygal K390
M_n (g/mol)	440	4800
Hydroxy groups per molecule	3	3
DP_n (PO) ^a	5	69
DP_n (EO) ^a	1	15

^aDP: degree of polymerization, represents the average number of ethylene oxide (EO) and propylene oxide (PO) units.

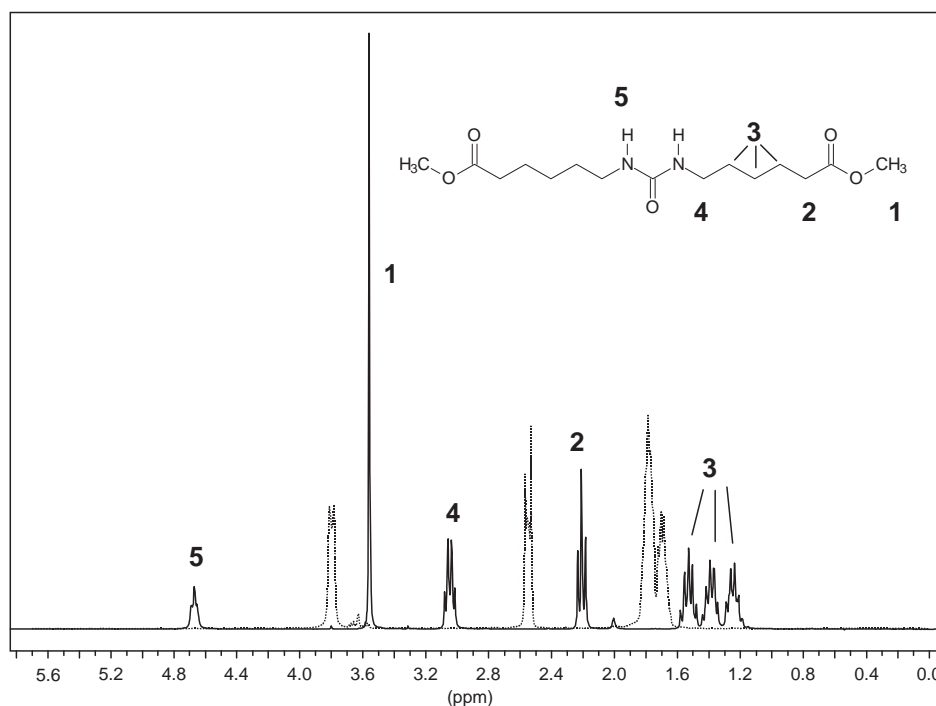


Fig. 2. ^1H -NMR spectrum of 6,6'-uretylene-di-hexanoic acid dimethyl ester (3a) and CBC (1) (dashed).

temperatures the elimination of caprolactame from CBC takes place. These reaction behavior cannot be excluded as side reaction for the curing step at 125°C. The resulting polymer networks were investigated with respect to their mechanical properties, thermal stability, degradation and swelling behavior and biocompatibility. The formulation of the different samples and the mechanical properties are listed in Table 2. The poly(ester–urea) samples are named PEU_x with *x* referring to the percentage of used PPO1. For comparison of polyurethane and CBC chemistry the mechanical data of sample PU0, a common polyurethane prepared from PPO2 as polyol and methylene diphenylene diisocyanate (Desmodur PU1806, Bayer AG) as diisocyanate are also listed in Table 2 [13].

The mechanical properties of PU0 and PEU0 are comparable. The CBC-based system shows a decreased Young's modulus and tensile strength at break. In contrast, the elongation at break increased. PEU0 and PEU10 show the same temperature stability as the corresponding PU0.

The mechanical properties of polyurethanes are primarily influenced by the used polyols. In analogy, we modified the polyol composition for the CBC formulations. The amount of low-molecular-weight polyol, PPO1 was increased from 0 to 100 wt% due to the amount of polyol. As shown in Table 2, the amount

of CBC was also raised with increasing amount of PPO1. The increasing amount of CBC causes difficulties in respect of miscibility at ambient temperature and viscosity of the formulations. Fig. 3 depicts the prepared samples. Phase separation, as observed for opaque samples, occurs at higher amounts of PPO1 (PEU 20, PEU 50). The phase separation was also detected by DSC measurements due to a second *T_g*. The temperature stability also decreased with increasing amount of PPO1 (Fig. 4).

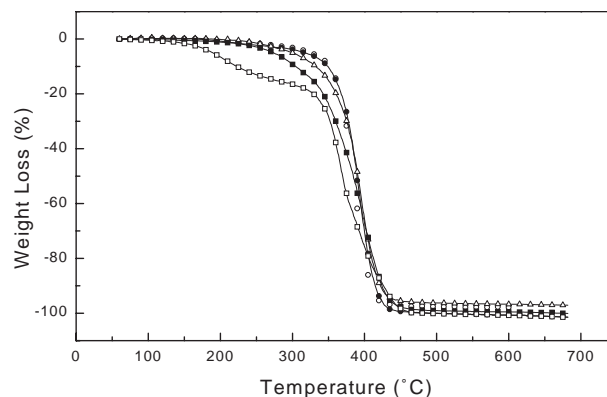


Fig. 4. TGA measurement of PEU0 (○), PEU10 (●), PEU20 (△), PEU50 (■), and PEU100 (□).

Table 2

Formulation and mechanical properties of the prepared poly(ester urea)s

Sample name	PU0	PEU0	PEU10	PEU20	PEU50	PEU100
Baygal K55 (wt%)	0	0	8.6	16	33	51.4
Baygal K390 (wt%)	91.9	92.7	77.2	64	33	0
CBC (wt%)	8.1 ^a	7.3	14.2	20	34	48.6
Appearance	Yellowish	Transparent	Transparent	Opaque	Opaque	Transparent
<i>T_g</i> (°C)	Nd	−61	−59	−60/−12	−59/−8	−20
TGA (°C) (5% weight loss)	314	325	317	300	274	189
Young's modulus (N/mm ²)	3.6	0.79	1.59	0.92	2.04	4.45
Tensile strength at break (N/mm ²)	0.8	0.52	0.54	0.62	1.02	0.90
Elongation at break (%)	65	134	50	127	82	26

Nd: not detected.

^aMethylene diphenylene diisocyanate (wt%).

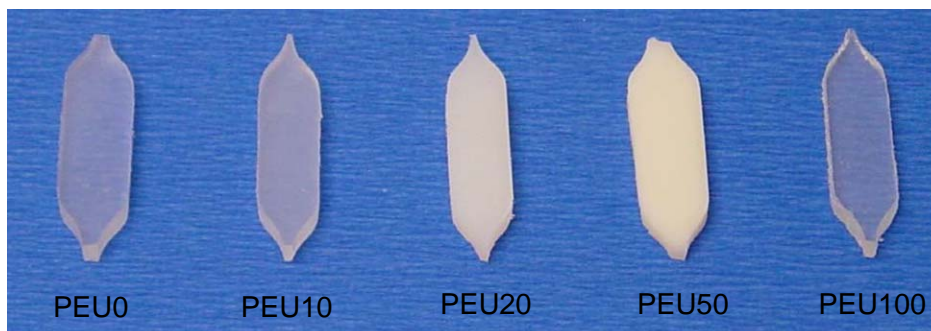


Fig. 3. Samples of the prepared networks.

The glass transition temperatures vary in dependence of the used polyol formulation. For PEU0 and PEU10 a T_g of -61°C and -59°C was determined. PEU100 shows a T_g of -20°C whereas the phase separated samples PEU20 and PEU50 show two T_g 's at -60°C , -12°C and -59°C , -8°C , respectively. TGA evidenced thermal stability up to 325°C (5% wt. loss) for Sample PEU0 (Fig. 4).

Swelling behavior and degradation [14] were studied by a general gravimetric method. Samples of the networks PEU0, PEU10, PEU20 and PEU100 were immersed in PBS (pH 7.4) and 0.1 N sodium hydroxide solution. After 10 days at 70°C , the water sorption of the sample in PBS was 9.7, 9.3, 13.4 and 9.1 wt%, respectively. The samples in the basic solution undergo degradation. The weight losses of the samples after 10 days are 18.3 wt% for PEU0, 17.4 wt% for PEU10, 31.0 wt% for PEU20, and 12.2 wt% for PEU100.

The comparison of the degradation rate due to the swelling behavior indicates a dependence of the degradation rate from the water sorption of the polymers (Fig. 5). The water sorption could be influenced by the used polyols. For this reason, the degradation rate can also be influenced by the polyol formulation.

4.3. Biocompatibility

We examined the ability of the polymerized CBC-polyol networks to support cell adhesion. Fibroblasts were seeded on the top of the hydrogel surface. After 4 days, the samples were stained with propidium iodide. The image (Fig. 6) of the PEU 0 sample shows that after seeding the cells spread on the polymer surfaces and gradually adhere to the polymer surface within a few hours. Continuous culture of fibroblasts on hydrogels for 4 days show that the fibroblasts retain their morphology similar to the cells grown on tissue culture polystyrene. Since the cells that adhere on the polymer surface remained healthy, PEU 0 and PEU 10 are considered to be non-toxic in vitro.

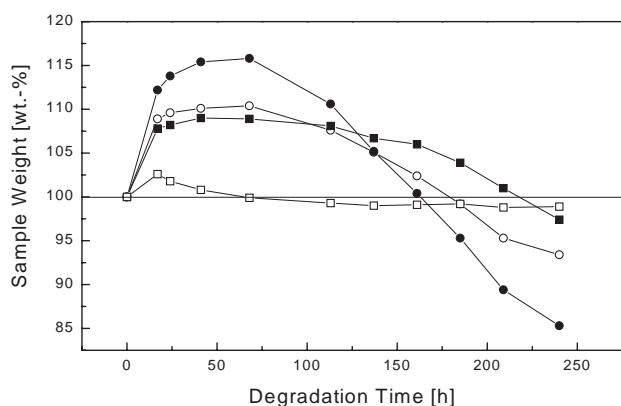


Fig. 5. Swelling and degradation of PEU0 (○), PEU10 (●), PEU20 (■), and PEU100 (□) in 0.1 N sodium hydroxide at 70°C .

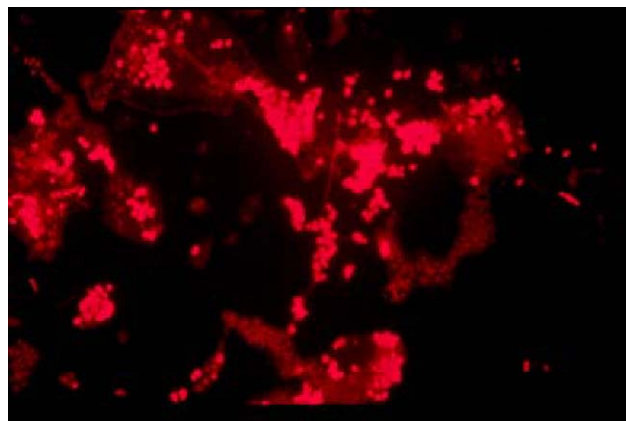


Fig. 6. Micrograph of adherent and spread fibroblasts on PEU0, Scale bar 200 μm .

5. Conclusion

A novel route for the isocyanate-free preparation of poly(ester-urea)s via the ring opening addition reaction of CBC and commercial polyols was investigated. In order to obtain information on the reaction mechanism, the conversion of CBC and alcohol with alcoholate catalysis was monitored by FT-IR, ^1H - and ^{13}C -NMR spectroscopy. The model reactions of CBC with methanol, ethanol and 2-propanol provided experimental evidence for the formation of the ester-urea by a ring opening addition reaction. CBC polyol formulations were mixed at room temperature with 4 mol% sodium alcoholate of the polyol and cured at 50°C for 10 min and 125°C for 12 h. The obtained poly(ester-urea) networks showed a thermal stability up to 325°C (5% wt. loss) and rubber-like mechanical properties.

The prepared polymers are degradable in 0.1 N sodium hydroxide solution. The rate of degradation depends on the swelling behavior. The degradation rate of the ester-urea increased with increasing water content of the polymer.

The ability of the polymerized poly(ester-urea)s to support cell adhesion and cell growth was examined. The polymer networks support cell adhesion and cell growth. Grown fibroblasts retain their morphology similar to the cells grown on tissue culture polystyrene. Therefore, we conclude that this novel synthetic material is non-toxic and offers attractive potential for tissue engineering applications. CBC represents an attractive and very versatile intermediate to produce polyurethanes, and polyureas, without requiring the use of isocyanates.

Mechanical properties, good biocompatibility and degradation behavior of poly(ester-urea)s make them interesting materials for the substitution of poly(ester urethane)s in medical applications.

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